

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁶ : C07D 403/14, 413/14, A61K 31/505, 31/535</p>	<p>A1</p>	<p>(11) International Publication Number: WO 99/61440 (43) International Publication Date: 2 December 1999 (02.12.99)</p>
<p>(21) International Application Number: PCT/US99/11455 (22) International Filing Date: 25 May 1999 (25.05.99) (30) Priority Data: 60/086,645 26 May 1998 (26.05.98) US (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): ADAMS, Jerry, Leroy [US/US]; 611 Forest Road, Wayne, PA 19087 (US). (74) Agents: DINNER, Dara, L. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).</p>		<p>(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: NOVEL SUBSTITUTED IMIDAZOLE COMPOUNDS (57) Abstract Novel 1,4,5-substituted imidazole compounds and compositions for use in therapy as ERK/MAP inhibitors of ERK/MAP mediated diseases.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KE	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

NOVEL SUBSTITUTED IMIDAZOLE COMPOUNDS

5

This invention relates to a novel group of imidazole compounds, processes for the preparation thereof, the use thereof in treating ERK/MAP mediated diseases and pharmaceutical compositions for use in such therapy.

10

There remains a need for treatment, in this field, for compounds which are capable of inhibiting the actions ERK/MAP kinase.

SUMMARY OF THE INVENTION

15

This invention relates to the novel compounds of Formula (I) and pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable diluent or carrier.

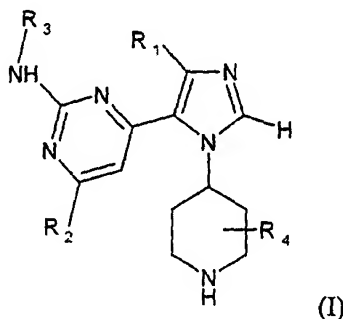
20

This invention relates to a method of treating a ERK/MAP kinase mediated disease, in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I).

This invention also relates to a method of inhibiting the ERK/MAP kinase in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I).

25

Accordingly, the present invention provides a compound of Formula (I):



R₁ is hydrogen, C₁₋₅ alkyl, halogen, C₁₋₅ alkoxy, or arylC₁₋₅ alkyl;

R₂ is hydrogen, C₁₋₅ alkyl, aryl, arylC₁₋₅ alkyl, heteroaryl, heteroarylC₁₋₅ alkyl, heterocyclic, heterocyclic C₁₋₅ alkyl;

30 R₃ is hydrogen, or C₁₋₃ alkyl;

R₄ is hydrogen, C₁₋₅ alkyl, aryl, arylC₁₋₅ alkyl, heteroaryl, heteroarylC₁₋₅ alkyl, heterocyclic, heterocyclic C₁₋₅ alkyl; or a pharmaceutically acceptable salt thereof.

5 **DETAILED DESCRIPTION OF THE INVENTION**

In Formula (I), suitable R₁ moieties include hydrogen, C₁₋₅ alkyl, halogen, C₁₋₅ alkoxy or arylC₁₋₅ alkyl. Preferably the moiety is a C₁₋₅ alkyl, which may be branched or unbranched.

10 Suitably, R₂ is hydrogen, C₁₋₅ alkyl, aryl, arylC₁₋₅ alkyl, heteroaryl, heteroarylC₁₋₅ alkyl, heterocyclic, heterocyclic C₁₋₅ alkyl, wherein all of these moieties may be optionally substituted as defined below.

When R₂ is a heterocyclic or heterocyclic alkyl moiety, the heterocyclic ring
15 is a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to pyrrolidiny, piperidine, morpholino, tetrahydropyran, tetrahydrothiopyran, tetrahydrothiopyransulfinyl, tetrahydrothiopyransulfonyl, pyrrolidiny, or an indole ring.

20 When R₂ is a heteroaryl or heteroarylalkyl moiety, the heteroaryl portion is a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazoliny, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, tetrazole, triazole, imidazole, or
25 benzimidazole.

Suitably, R₃ is hydrogen, or C₁₋₃ alkyl (branched or unbranched).

30 Suitably, R₄ is hydrogen, C₁₋₅ alkyl, aryl, arylC₁₋₅ alkyl, heteroaryl, heteroarylC₁₋₅ alkyl, heterocyclic, heterocyclic C₁₋₅ alkyl, and wherein all of these moieties may be optionally substituted as defined below. Suitable heteroaryl and heterocyclic containing moieties for use herein are the same as those described above for R₂.

35

As used herein, "optionally substituted" unless specifically defined shall mean such groups as halogen, such as fluorine, chlorine, bromine or iodine; hydroxy;

hydroxy substituted C₁₋₁₀alkyl; C₁₋₁₀ alkoxy, such as methoxy or ethoxy; halosubstituted C₁₋₁₀ alkoxy; S(O)_m alkyl, wherein m is 0, 1 or 2, such as methyl thio, methylsulfinyl or methyl sulfonyl; amino, mono & di-C₁₋₅ alkyl substituted amino, such as the moiety R₇R₁₇ wherein R₇ and R₁₇ are hydrogen or C₁₋₅ alkyl, or where the R₇ and R₁₇ substituent groups may together with the nitrogen to which they are attached cyclize to form a 5 to 7 membered ring which optionally includes an additional heteroatom selected from O/N/S; C₁₋₁₀ alkyl, C₃₋₇ cycloalkyl, or C₃₋₇cycloalkyl C₁₋₁₀ alkyl group, such as methyl, ethyl, propyl, isopropyl, t-butyl, etc. or cyclopropyl methyl; halosubstituted C₁₋₁₀ alkyl, such CF₂CF₂H, or CF₃; an optionally substituted aryl, such as phenyl, or an optionally substituted arylalkyl, such as benzyl or phenethyl, wherein these aryl moieties may also be substituted one to two times by halogen; hydroxy; hydroxy substituted alkyl; C₁₋₁₀ alkoxy; S(O)_malkyl; amino, mono & di-substituted amino, such as in the NR₇R₁₇ group; alkyl, or CF₃.

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonic acid, ethane sulphonic acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of Formula (I) may also be formed with a pharmaceutically acceptable cation, for instance, if a substituent group comprises a carboxy moiety. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

25

The following terms, as used herein, refer to:

- "halo" or "halogens", include the halogens: chloro, fluoro, bromo and iodo.
- "C₁₋₅alkyl" or "alkyl" - includes both straight and branched chain radicals of 1 to 5 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl and the like.
- The term "cycloalkyl" is used herein to mean cyclic radicals, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.
- "aryl" - phenyl and naphthyl;
- "heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or "heteroaryl alkyl") - a 5-10 membered aromatic ring system in which one or more

rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, thiazole, thiadiazole, tetrazole, triazole, imidazole, or benzimidazole.

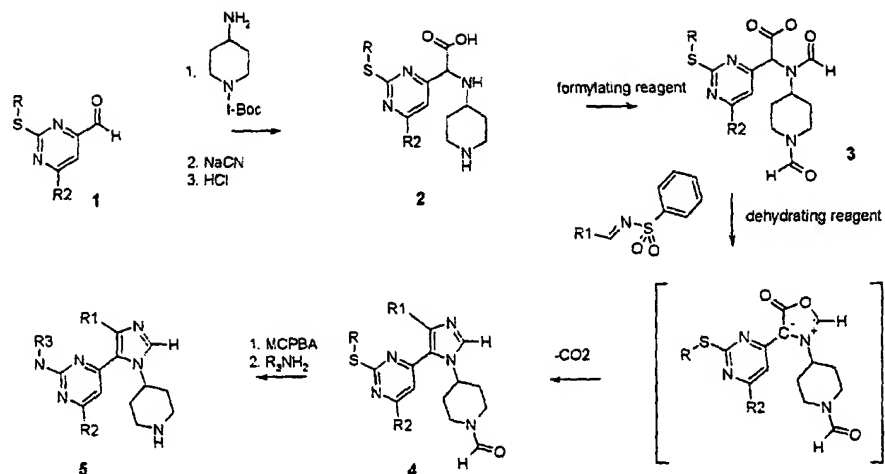
- 5 • "heterocyclic" (on its own or in any combination, such as "heterocyclalkyl") - a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine, tetrahydropyran, or imidazolidine.
- 10 • The term "alkyl" or "heteroarylalkyl" or "heterocyclalkyl" is used herein to mean C₁₋₄ alkyl as defined above attached to an aryl, heteroaryl or heterocyclic moiety as also defined herein unless otherwise indicate.

It is recognized that the compounds of the present invention may exist as stereoisomers, regioisomers, or diastereoisomers. These compounds may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds are included within the scope of the present invention.

20 Exemplified compounds of Formula (I) include:
1-(4-Piperidinyl)-4-methyl-5-(3-amino-pyrimidin-4-yl)imidazole; or a pharmaceutically acceptable salt thereof.

The compounds of Formula (I) may be obtained by applying synthetic procedures, some of which are illustrated in the Schemes herein. The synthesis provided for in these Schemes is applicable for the producing compounds of Formula (I) having a variety of different R₁, R₂, R₃, and R₄ groups which are reacted, employing optional substituents which are suitably protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed.

Suitable protecting groups for use with the imidazole nitrogen are well known in the art and described in many references, for instance, Protecting Groups in Organic Synthesis, Greene T W, Wiley-Interscience, New York, 1981. Preferably an example of an imidazole nitrogen protecting group is tetrahydropyranyl.



SCHEME 1

- The synthesis of 4-formyl-2-thioalkylpyrimidine ($R = \text{Pr}$, $R_2 = \text{H}$) **1**, is described in US Patent 5,658,903, whose disclosure is incorporated herein by reference in its entirety. Formation of the imine of **1** with t-Boc-4-aminopiperidine under dehydrating conditions, for example MgSO_4 in CH_2Cl_2 , followed by addition of cyanide affords the α -aminonitrile. Hydrolysis of the nitrile under acidic conditions yields the deprotected free amino acid **2**. Formylation using the mixed anhydride of formic and acetic acids, or some other suitable formulating agent, provides the required precursor **3**, for the 1,3-dipolar cycloaddition. Isolation of **3** may not be required as under the dehydrating conditions described for the formylation of **2**, cyclodehydration to form the intermediate munchnone may occur. Reaction of the thus formed munchnone with a sulfonylimine (formed by condensation of the sulfonamide with $R_2\text{COH}$) provides the imidazole cycloaddition adduct, **4**. The general procedures for this chemistry and the specific application for the formation of imidazoles are described in Consonni, R. et. al. *J. Chem. Research* (S) p188 (1991) and Croce, P.D., et. al. *J. Heterocyclic Chem.* 24, 1793 (1987). Oxidation of the 2-thioalkylpyrimidine to the more activated sulfoxide and/or sulfone leaving group allows facile displacement of the sulfur with a variety of nucleophiles, including ammonia and simple alkyl amines (R_3), to afford the desired 2-aminopyrimidines, **5**.

Pharmaceutically acid addition salts of compounds of Formula (I) may be obtained in known manner, for example by treatment thereof with an appropriate amount of acid in the presence of a suitable solvent.

METHODS OF TREATMENT

The compounds of Formula (I) or a pharmaceutically acceptable salt thereof can be used in the manufacture of a medicament for the prophylactic or therapeutic treatment of an ERK kinase mediated disease state in a human, or other mammal, which is exacerbated or caused by excessive or unregulated ERK2/MAP kinase activation by such mammal's cell, such as but not limited to monocytes and/or macrophages.

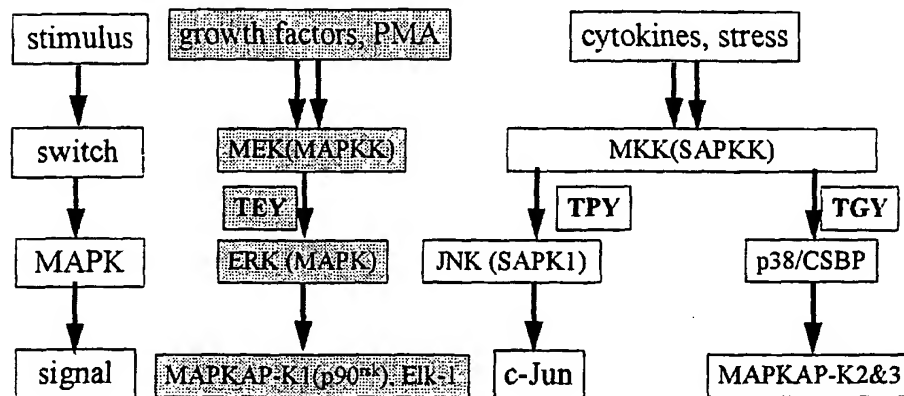
Intracellular signal transduction is the means by which cells respond to extracellular stimuli. Regardless of the nature of the cell surface receptor (e. g. protein tyrosine kinase or seven-transmembrane G-protein coupled), protein kinases and phosphatases along with phospholipases are the essential machinery by which the signal is further transmitted within the cell [Marshall, J.C. Cell, 80, 179-278 (1995)]. Protein kinases can be categorized into five classes with the two major classes being tyrosine kinases and serine / threonine kinases depending upon whether the enzyme phosphorylates its substrate(s) on specific tyrosine(s) or serine / threonine(s) residues [Hunter, T. Methods in Enzymology (Protein Kinase Classification) p. 3, Hunter, T.; Sefton, B. M.; eds. vol. 200, Academic Press; San Diego, 1991].

The MAP kinase or ERK (extracellular signal regulated kinase) family is a novel set of kinases which are intimately involved with and in many cases required for the intracellular transmission of mitogenic or growth signals. ERK1 and ERK2 were the first two members of the family to be identified. A characteristic requirement for activation of these kinases is the dual phosphorylation on the TEY sequence of the kinase activation loop, a reaction which is effected by a select group of upstream kinases, know as MAP kinase kinases (MAPKK). Additional signal transduction components both upstream and downstream of ERK1/ERK2 have been identified and pathway(s) leading from activation of an extracellular receptor to transcriptional regulation have been elucidated. [Marshall, C. J. Cell, 80, 179 (1995); Herskowitz, I. Cell, 80, 187 (1995); Hunter, T. Cell, 80, 225 (1995); Seger, R., and Krebs, E.G. FASEB J., 726-735 (1995)]. A general outline of this sequence for the ERK kinases and related MAP kinases is shown in figure 1. The ERK2 kinase may also be referred to as p44MAP kinase.

The JNK and p38 kinases constitute two additional arms of the MAP kinase pathway which are primarily activated by "stress" signals. All three pathways are independent and are composed of additional family members. Although independent

- there is considerable crosstalk between the pathways and in most cases an extracellular signal will activate several parts of the pathway; hence is the unique pattern and strength of the signals which emerge from these kinase cascades which will influence the cellular response. The different MAP family members are
- 5 distinguished by the identify of the dual activation sequence. The JNK kinases contain TPY and the p38 kinases TGY, whereas as noted earlier the ERK kinases contain TEY.

MAP Kinase Family: General Features



10

Figure 1

- Growth or mitogenic signals are the most important activators of the ERK kinases and considerable evidence supports the requirement of ERK signaling for response to these stimuli (Figure 2 illustrates a more detailed description of the ERK1/ERK2 cascade). Hence inhibition of the ERK kinase has potential for
- 15 therapeutic utility in a number of disease states, most importantly to block the uncontrolled growth of cancer cells. Other potential utilities of ERK kinase inhibitors are inflammation, allergy, autoimmune disease and neurodegeneration (figure 2).

20

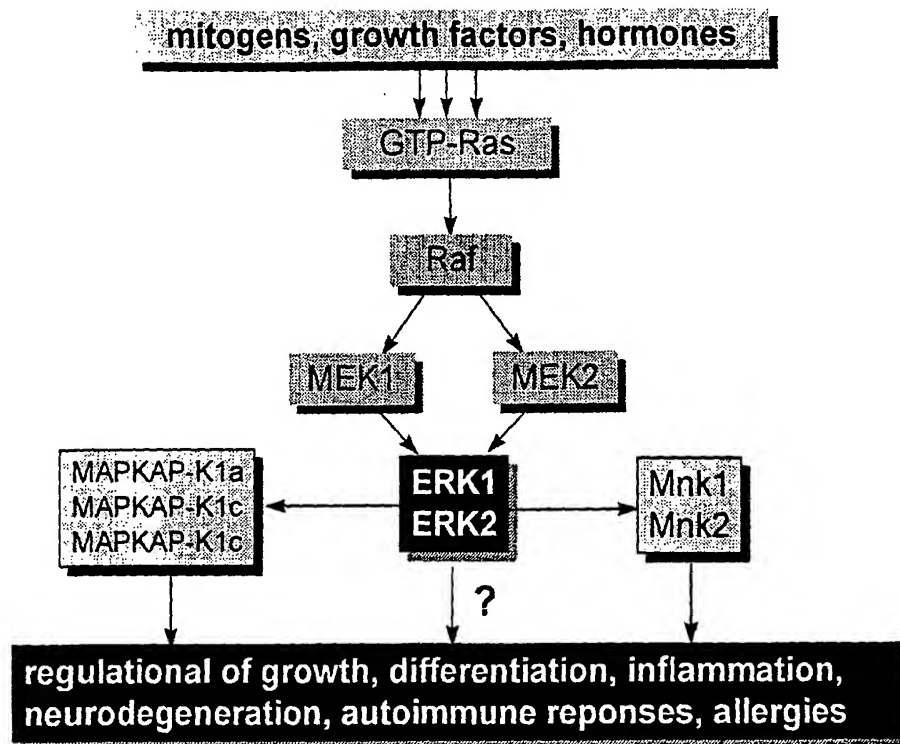


Figure 2

5 The compounds of Formula (I) may also be used topically in the treatment or prophylaxis of topical disease states mediated by or exacerbated by excessive ERK/MAP kinase production, such as inflamed joints, eczema, psoriasis and other inflammatory skin conditions such as sunburn; inflammatory eye conditions including conjunctivitis; pyresis, pain and other conditions associated with inflammation.

10 The compounds of Formula (I) are administered in an amount sufficient to inhibit ERK/MAP activity such that it is regulated down to normal levels, or in some case to subnormal levels, so as to ameliorate or prevent the disease state.

15 The discovery that the compounds of Formula (I) are inhibitors of ERK/MAP may be based upon the effects of the compounds of Formulas (I) on *in vitro* assays which are described herein.

As used herein, the term "inhibiting the activity ERK/MAP kinase refers to:

- a) a decrease of excessive *in vivo* levels of the kinase in a human to normal or sub-normal levels by inhibition of the *in vivo* release of the kinase by all cells, including but not limited to monocytes or macrophages;
- 5 b) a down regulation, at the genomic level, of excessive *in vivo* levels of the kinase in a human to normal or sub-normal levels;
- c) a down regulation, by inhibition of the direct synthesis of the kinase as a posttranslational event; or
- d) a down regulation, at the translational level, of excessive *in vivo* levels of
10 the kinase in a human to normal or sub-normal levels.

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof in therapy, it will normally be formulated into a pharmaceutical composition in accordance with standard pharmaceutical practice. This invention,
15 therefore, also relates to a pharmaceutical composition comprising an effective, non-toxic amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent.

Compounds of Formula (I), pharmaceutically acceptable salts thereof and
20 pharmaceutical compositions incorporating such may conveniently be administered by any of the routes conventionally used for drug administration, for instance, orally, topically, parenterally or by inhalation. The compounds of Formula (I) may be administered in conventional dosage forms prepared by combining a compound of Formula (I) with standard pharmaceutical carriers according to conventional
25 procedures. The compounds of Formula (I) may also be administered in conventional dosages in combination with a known, second therapeutically active compound. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation. It will be appreciated that the form and character of the pharmaceutically acceptable character or diluent is dictated
30 by the amount of active ingredient with which it is to be combined, the route of administration and other well-known variables. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the Formulation and not deleterious to the recipient thereof.

35 The pharmaceutical carrier employed may be, for example, either a solid or liquid. Exemplary of solid carriers are lactose, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid and the like. Exemplary of liquid

carriers are syrup, peanut oil, olive oil, water and the like. Similarly, the carrier or diluent may include time delay material well known to the art, such as glyceryl mono-stearate or glyceryl distearate alone or with a wax.

5 A wide variety of pharmaceutical forms can be employed. Thus, if a solid carrier is used, the preparation can be tableted, placed in a hard gelatin capsule in powder or pellet form or in the form of a troche or lozenge. The amount of solid carrier will vary widely but preferably will be from about 25mg. to about 1g. When a liquid carrier is used, the preparation will be in the form of a syrup, emulsion, soft
10 gelatin capsule, sterile injectable liquid such as an ampule or nonaqueous liquid suspension.

 Compounds of Formula (I) may be administered topically, that is by non-systemic administration. This includes the application of a compound of Formula (I)
15 externally to the epidermis or the buccal cavity and the instillation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

20 Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by
25 weight of the formulation. It may however comprise as much as 10% w/w but preferably will comprise less than 5% w/w, more preferably from 0.1% to 1% w/w of the formulation.

 Lotions according to the present invention include those suitable for
30 application to the skin or eye. An eye lotion may comprise a sterile aqueous solution optionally containing a bactericide and may be prepared by methods similar to those for the preparation of drops. Lotions or liniments for application to the skin may also include an agent to hasten drying and to cool the skin, such as an alcohol or acetone, and/or a moisturizer such as glycerol or an oil such as castor oil or arachis oil.

35 Creams, ointments or pastes according to the present invention are semi-solid formulations of the active ingredient for external application. They may be made by

mixing the active ingredient in finely-divided or powdered form, alone or in solution or suspension in an aqueous or non-aqueous fluid, with the aid of suitable machinery, with a greasy or non-greasy base. The base may comprise hydrocarbons such as hard, soft or liquid paraffin, glycerol, beeswax, a metallic soap; a mucilage; an oil of
5 natural origin such as almond, corn, arachis, castor or olive oil; wool fat or its derivatives or a fatty acid such as steric or oleic acid together with an alcohol such as propylene glycol or a macrogel. The formulation may incorporate any suitable surface active agent such as an anionic, cationic or non-ionic surfactant such as a sorbitan ester or a polyoxyethylene derivative thereof. Suspending agents such as
10 natural gums, cellulose derivatives or inorganic materials such as siliceous silicas, and other ingredients such as lanolin, may also be included.

Drops according to the present invention may comprise sterile aqueous or oily solutions or suspensions and may be prepared by dissolving the active ingredient in a
15 suitable aqueous solution of a bactericidal and/or fungicidal agent and/or any other suitable preservative, and preferably including a surface active agent. The resulting solution may then be clarified by filtration, transferred to a suitable container which is then sealed and sterilized by autoclaving or maintaining at 98-100°C. for half an hour. Alternatively, the solution may be sterilized by filtration and transferred to the
20 container by an aseptic technique. Examples of bactericidal and fungicidal agents suitable for inclusion in the drops are phenylmercuric nitrate or acetate (0.002%), benzalkonium chloride (0.01%) and chlorhexidine acetate (0.01%). Suitable solvents for the preparation of an oily solution include glycerol, diluted alcohol and propylene glycol.

25
Compounds of Formula (I) may be administered parenterally, that is by intravenous, intramuscular, subcutaneous intranasal, intrarectal, intravaginal or intraperitoneal administration. The subcutaneous and intramuscular forms of parenteral administration are generally preferred. Appropriate dosage forms for such
30 administration may be prepared by conventional techniques. Compounds of Formula (I) may also be administered by inhalation, that is by intranasal and oral inhalation administration. Appropriate dosage forms for such administration, such as an aerosol formulation or a metered dose inhaler, may be prepared by conventional techniques.

35
For all methods of use disclosed herein for the compounds of Formula (I), the daily oral dosage regimen will preferably be from about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to 30 mg/kg, more preferably from

about 0.5 mg to 15mg. The daily parenteral dosage regimen about 0.1 to about 80 mg/kg of total body weight, preferably from about 0.2 to about 30 mg/kg, and more preferably from about 0.5 mg to 15mg/kg. The daily topical dosage regimen will preferably be from 0.1 mg to 150 mg, administered one to four, preferably two or three times daily. The daily inhalation dosage regimen will preferably be from about 0.01 mg/kg to about 1 mg/kg per day. It will also be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages of a compound of Formula (I) or a pharmaceutically acceptable salt thereof will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular patient being treated, and that such optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses of a compound of Formula (I) or a pharmaceutically acceptable salt thereof given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

The novel compounds of Formula (I) may also be used in association with the veterinary treatment of mammals, other than humans, in need of inhibition of ERK/MAP kinase inhibition or production.

The invention will now be described by reference to the following biological examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention.

BIOLOGICAL EXAMPLES

The ERK/MAP inhibiting effects of compounds of the present invention are determined by the following *in vitro* assay:

The ERK kinase assay was performed using a commercially available kit (P44^{MPK}, Upstate Biotechnology Inc.) Kinase activity was determined by measuring the incorporation of ³²P from γ-[³²P]ATP into an EGFR-derived peptide (T669) having the following sequence: KRELVEPLTPSGEAPNQALLR. Reactions (30 μl) contained 25 mM Hepes buffer, pH 7.4, 8 mM MgCl₂; 10 μM Na-vanadate; 1 mM EDTA, 0.8 μCi/170 μM ³²P/ATP; 0.4 ng ERK kinase; and 0.4 mM peptide. Compounds were incubated for 20 min at 4 °C with enzyme and peptide prior to adding ATP. Reactions were incubated for 10 min at 30 °C and were stopped by adding 10 μL of 0.3 M phosphoric acid. Phosphorylated peptide was isolated from the reaction mixture on phosphocellulose filter paper (p81).

Filters were washed with 75 mM phosphoric acid and counted using a liquid scintillation counter.

SYNTHETIC EXAMPLES

5 The invention will now be described by reference to the following examples which are merely illustrative and are not to be construed as a limitation of the scope of the present invention. All temperatures are given in degrees centigrade, all solvents are highest available purity and all reactions run under anhydrous conditions in an argon atmosphere unless otherwise indicated.

10

 In the Examples, all temperatures are in degrees Centigrade (°C). Mass spectra were performed upon a VG Zab mass spectrometer using fast atom bombardment or on a micromass platform electrospray ionization mass spectrometer in the positive ion mode using 95:5 CH₃CN/CH₃OH with 1 % formic acid as the carrier solvent, unless otherwise indicated. ¹H-NMR (hereinafter "NMR") spectra were recorded at 250 MHz using a Bruker AM 250 or Am 400 spectrometer. Multiplicities indicated are: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and br indicates a broad signal. Sat. indicates a saturated solution, eq indicates the proportion of a molar equivalent of reagent relative to the principal reactant. Flash chromatography is run over Merck Silica gel 60 (230 - 400 mesh).

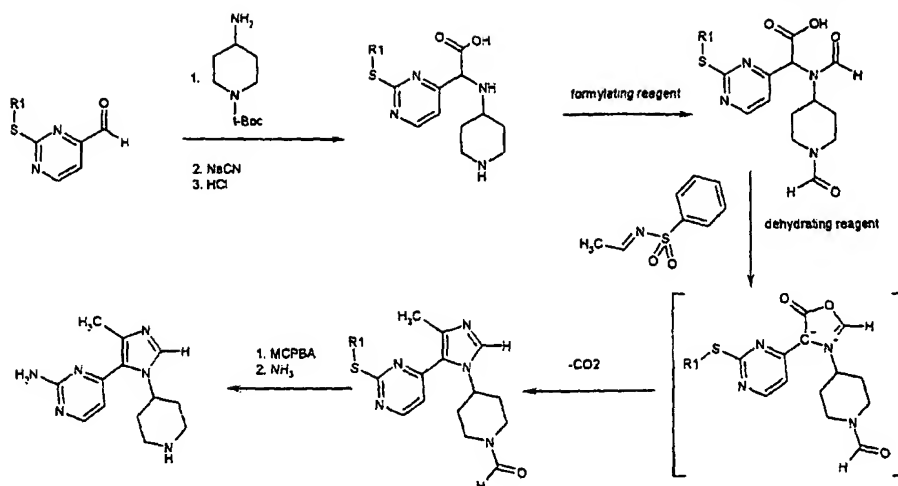
20

Example 1

1-(4-Piperidinyl)-4-methyl-5-(3-amino-pyrimidin-4-yl)imidazole

 The title compound can be prepared by the synthetic route illustrated in Scheme 2 using the reaction conditions described in Consonni, R. et. al. J.Chem. Research (S) p188 (1991) and Croce, P.D., et. al.. J. Heterocyclic Chem. 24, 1793 (1987) or modifications thereof which are apparent to one skilled in the art of organic synthesis. The synthesis of the requisite starting pyrimidine aldehyde and the t-Boc-4-aminopiperidine are described in US Patent 5,670,527 whose disclosure is incorporated herein by reference in its entirety.

30

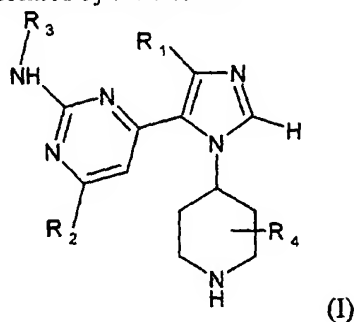


Scheme 2

- 5 All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.
- 10 The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore, the Examples
- 15 herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is Claimed is:

1. A compound represented by the formula :



- 5 wherein
- R₁ is hydrogen, halogen, C₁₋₅ alkyl, C₁₋₅ alkoxy, or arylC₁₋₅ alkyl;
- R₂ is hydrogen, C₁₋₅ alkyl, aryl, arylC₁₋₅ alkyl, heteroaryl, heteroarylC₁₋₅ alkyl, heterocyclic, or heterocyclic C₁₋₅alkyl, and wherein all of these moieties may be optionally substituted;
- 10 R₃ is hydrogen, or C₁₋₃ alkyl;
- R₄ is hydrogen, C₁₋₅ alkyl, aryl, arylC₁₋₅ alkyl, heteroaryl, heteroarylC₁₋₅ alkyl, heterocyclic, or heterocyclic C₁₋₅ alkyl, and wherein all of these moieties may be optionally substituted;
- or a pharmaceutically acceptable salt thereof.
- 15
2. The compound according to Claim 1 wherein R₁ is a C₁₋₅ alkyl.
3. The compound according to Claim 2 wherein R₂ is hydrogen or a heterocyclic or heterocyclic alkyl ring.
- 20
4. The compound according to Claim 2 wherein R₃ is hydrogen.
5. The compound according to Claim 2 wherein R₄ is hydrogen.
- 25
6. A pharmaceutical composition comprising an effective amount of a compound according to any of Claims 1 to 5 and a pharmaceutically acceptable carrier or diluent.

7. A method of treating an ERK/MAP kinase mediated disease in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I) according to any of Claims 1 to 6.
- 5 8. The method according to claim 7 wherein the mammal is afflicted with a ERK/MAP kinase mediated disease selected from psoriatic arthritis, Reiter's syndrome, rheumatoid arthritis, gout, traumatic arthritis, rubella arthritis and acute synovitis, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic condition, sepsis, septic shock, endotoxic shock, gram negative
- 10 sepsis, toxic shock syndrome, Alzheimer's disease, stroke, neurotrauma, asthma, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcososis, bone resorption disease, osteoporosis, restenosis, cardiac and renal reperfusion injury, thrombosis, glomerularonephritis, diabetes, graft vs. host reaction, allograft rejection, inflammatory bowel disease,
- 15 Crohn's disease, ulcerative colitis, multiple sclerosis, muscle degeneration, eczema, contact dermatitis, psoriasis, sunburn, or conjunctivitis.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/11455

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07D 403/14, 413/14; A61K 31/505, 31/535

US CL :544/122, 284, 295, 296, 331; 514/235.8, 252, 259, 275

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 544/122, 284, 295, 296, 331; 514/235.8, 252, 259, 275

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONEElectronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE, APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A, P	WANG et al. Structural basis of inhibitor selectivity in MAP kinases. Structure. 18 September 1998, Vol. 6, No. 9, pages 1117-1128.	1-5
A	US 5,593,992 A (ADAMS et al) 14 January 1997, see entire document.	1-5



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
B earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*A* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

01 JULY 1999

Date of mailing of the international search report

29 SEP 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer

ANN M. KESINGER

Telephone No. (703) 305-1878

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/11455**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claims Nos.: 6-8
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.